Comorbidities in adults with asthma

Weatherburn, Christopher J.; Guthrie, Bruce; Mercer, Stewart W.; Morales, Daniel R.

Published in:
Clinical and Experimental Allergy

DOI:
10.1111/cea.12971

Publication date:
2017

Document Version
Peer reviewed version

DR DANIEL R MORALES (Orcid ID : 0000-0002-0063-8069)

Article type : Original Article-Asthma and Rhinitis

Comorbidities in adults with asthma: population-based cross-sectional analysis of 1.4 million adults in Scotland

Dr Christopher J Weatherburn. Division of Population Health Sciences, School of Medicine, University of Dundee, Dundee, UK

Prof Bruce Guthrie. Division of Population Health Sciences, School of Medicine, University of Dundee, UK

Prof Stewart W Mercer. General Practice and Primary Care, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK

Dr Daniel R Morales. Division of Population Health Sciences, School of Medicine, University of Dundee, Dundee, UK

SHORT TITLE

Comorbidities in adults with asthma

CORRESPONDING AUTHOR

Dr Daniel R Morales, Quality, Safety & Informatics Group, Division of Population Health Sciences, School of Medicine, University of Dundee, Mackenzie Building, Dundee, DD2 4BF, UK

TEL: +44-1382-383706 E-mail: d.r.z.morales@dundee.ac.uk, danielmorales@nhs.net

WORD COUNT: Abstract = 248, Manuscript = 3017

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cea.12971

Abstract

Background: Comorbidity in people with asthma can significantly increase asthma morbidity and lower adherence to asthma guidelines.

Objective: The objective of this study was to comprehensively measure the prevalence of physical and mental health comorbidities in adults with asthma using a large nationally representative population.

Methods: Cross-sectional analysis of routine primary care electronic medical records for 1,424,378 adults in the UK, examining the prevalence of 39 comorbidities in people with and without asthma, before and after adjustment for age, sex, social deprivation and smoking status using logistic regression.

Results: Of 39 comorbidities measured, 36 (92%) were significantly more common in adults with asthma. 62.6% of adults with asthma had ≥1 comorbidity vs. 46.2% of those without, and 16.3% had ≥4 comorbidities vs. 8.7% of those without. Comorbidities with the largest absolute increase in prevalence in adults with asthma were: COPD (13.4% vs 3.1%), depression (17.3% vs 9.1%), painful conditions (15.4% vs 8.4%), and dyspepsia (10.9% vs 5.2%). Comorbidities with the largest relative difference in adults with asthma compared to without were: COPD (adjusted odds ratio [aOR] 5.65, 95%CI 5.52-5.79), bronchiectasis (aOR 4.65, 95%CI 4.26-5.08), eczema/psoriasis (aOR 3.30, 95%CI 3.14-3.48), dyspepsia (aOR 2.20, 95%CI 2.15-2.25) and chronic sinusitis (aOR 2.12, 95%CI 1.99-2.26). Depression and anxiety were more common in adults with asthma (aOR 1.60, 95%CI 1.57-1.63, and aOR 1.53, 95%CI 1.48-1.57 respectively).

Conclusions and Clinical Relevance: Physical and mental health comorbidity is the norm in adults with asthma. Appropriate recognition and management should form part of routine asthma care.

Introduction

Asthma is a worldwide public health problem associated with a high economic cost and is the second most common chronic illness in primary care with 6.0% of the UK population being actively treated.[1][2] Comorbidities are important to recognise in people with asthma because they can complicate the clinical care of patients with asthma in a variety of ways.[3][4] First comorbidities may present with similar symptoms as those associated with poor asthma control. This could lead to under or overtreatment of asthma through misdiagnosis, increasing treatment burden and unnecessary cost.[5] Second, potentially beneficial effects of treatment for some comorbidities may be withheld in people with asthma due to safety concerns, such as beta-blockers for the management of cardiovascular disease or anxiety.[6][7] Third, people living with asthma may be at increased risk of developing other conditions, which may lower adherence to asthma therapy and increase asthma morbidity. For example, comorbid depression or anxiety may lead to poorer asthma outcomes and is associated with increasing asthma severity.[8][9] In many instances, the importance of these problems in absolute terms is directly related to the prevalence of the comorbidity of interest in people with asthma.

Existing studies investigating the prevalence of comorbidity in people with asthma have typically measured a limited number of comorbidities, used small population samples, or have not always adjusted for important confounders, such as smoking and social deprivation, which are strongly associated with the number of physical and mental health comorbidities.[10] Understanding patterns of comorbidity in adults with asthma is therefore important to help health care professionals contextualise asthma care, not least because recommended treatments based on evidence from clinical trials typically include selected populations whose narrow age and eligibility criteria mean that many people with comorbidity may be excluded. For example Travers et al found that 64-100% (median 96%) of people with spirometry or peak flow variability defined asthma identified from a population survey would have been excluded from 17 key asthma trials

underpinning the Global Initiative for Asthma (GINA) guidelines.[11] This is important because a medicines benefit risk balance may be less favourable in people with certain comorbidities such as the cardiovascular risk from beta2-agonists.[12] The aim of this study was therefore to measure the prevalence of comorbid physical and mental health conditions in people with asthma and to compare this with a general population of adults without asthma, adjusting for confounders including age, gender, smoking and social deprivation.

Methods

Data source

The design was a cross-sectional analysis of an established database containing electronic medical records for 1,424,378 adults aged 18 and over from 314 primary care practices in Scotland, UK on 31st March 2007. The UK National Health Service (NHS) requires registration with a single primary care practice, and 98% of people in Scotland are registered with a general practice. The data covers approximately one third of the Scottish population, and is nationally representative in terms of age, sex and socioeconomic deprivation.[13]

Asthma definition

People with active asthma aged 18 and over were identified by them having a Read Code for asthma ever recorded ever, no recent Read Code for asthma resolved, and having been prescribed one or more asthma medications in the 12 months prior to data extraction. This definition matches that used in the UK Quality and Outcomes Framework, a national programme which incentivises practices to maintain disease registers for selected conditions including asthma, used to define asthma are shown in the online supporting information appendix 1.

Other morbidities

Data on 39 common and important comorbidities were extracted as described previously (please refer to appendix table for details of selection process).[14] Data were extracted on age, sex, smoking status and socioeconomic deprivation measured using the Carstairs deprivation score. The Carstairs score is a measure of neighbourhood socioeconomic deprivation assigned to individuals based on their postcode of residence, and has been widely used in healthcare research.[15][16]

Statistical analysis

The prevalence of each of the 39 different comorbidities was measured in people with and without asthma. Univariate and multivariate logistic regression was used to estimate odds ratios with 95% confidence intervals (95%CI) for the prevalence of each of 31 physical conditions in adults with asthma compared to the general adult population, adjusted for age, sex, smoking status and socioeconomic deprivation measured by quintiles (equal fifths of the Scottish population) of the Carstairs score. This analysis was repeated for eight mental health conditions, with a further adjustment for the total number of physical conditions since physical disease burden is known to be strongly associated with the presence of depression.[14] All general practices contributing data gave explicit permission to use the anonymised data for research and the NHS Grampian Research Ethics Committee had agreed that individual studies did not require ethical approval. Data were analysed using IBM SPSS v22.

Results

Of 1,424,378 adults in the dataset, 84,505 had active asthma (prevalence = 5.9%, 95% CI 5.89 to 5.97). The characteristics of adults with and without asthma are shown in table 1. A larger proportion of adults with asthma were women (58.7% vs 50.4% without), were non-smokers and were living in more deprived areas.

Comorbidities in adults with asthma

The crude prevalence of comorbidity was significantly greater in people with asthma compared to the general population. The crude prevalence of people with one or more health condition was 62.6% in adults with asthma compared to only 46.2% in those without asthma (table 1). The crude prevalence of people with ≥4 health conditions was 16.3% in people with asthma compared to 8.7% in those without. In unadjusted analysis, adults with asthma had on average 1.6 more comorbid health conditions (95% CI 1.59 to 1.62, p<0.0001) compared to adults without asthma.

The crude prevalence of physical and mental health conditions in adults with and without asthma are shown in tables 2 and 3. The crude prevalence of the most frequently recorded comorbidities in adults with asthma in order of frequency were: hypertension (20.1%), depression (17.3%), pain (15.9%), COPD (13.4%) and dyspepsia (10.9%). Comorbidities with the greatest absolute percentage difference in prevalence in people with asthma compared to adults without, in order of frequency were: COPD (absolute percentage difference [APD] 10.3%, 95%CI 19.1 to 10.5), depression (APD 8.2%, 95%CI 7.4 to 7.9), painful conditions (APD 7.5%, 95%CI 7.2 to 7.7), dyspepsia (APD 5.7%, 95%CI 5.5 to 5.9) and hypertension (APD 3.9%, 95%CI 3.6 to 4.2).

Following adjustment for age, sex, deprivation and smoking status, 29 (94%) of the 31 physical comorbidities and 7 (88%) of the 8 mental health comorbidities were significantly more common in adults with asthma compared to those without (table 2 and 3 respectively). In relative terms, the comorbidities most likely to be present in adults with asthma compared to adults in the general population following multivariate adjustment were: COPD (adjusted OR [aOR] 5.65, 95%CI 5.52 to 5.79), bronchiectasis (aOR 4.65, 95%CI 4.26 to 5.08), eczema/psoriasis (aOR 3.30, 95%CI 3.14 to 3.48), dyspepsia (aOR 2.20, 95%CI 2.15 to 2.25) and chronic sinusitis (aOR 2.12 95%CI 1.99 to 2.26). Additionally, adults with asthma were also more likely to have other important physical comorbidities not classically associated with asthma including pain (aOR 2.04, 95%CI 1.99 to 2.08),

migraine (aOR 1.97, 95%CI 1.85 to 2.10), heart failure (aOR 1.47, 95%CI 1.39 to 1.55), coronary heart disease (aOR 1.39, 95%CI 1.35 to 1.43) and epilepsy (aOR 1.29, 95%CI 1.21 to 1.38).

Of the mental health conditions examined, people with asthma were significantly more likely to have depression (aOR 1.60, 95%CI 1.57 to 1.63) and anxiety (aOR 1.53, 95%CI 1.48 to 1.57). Associations with other mental health conditions were weaker, and only dementia had a significantly lower likelihood of being recorded in adults with asthma than those without (aOR 0.60, 95%CI 0.55 to 0.66).

Discussion

This study investigating the prevalence of comorbidity in adults with asthma using a large nationally representative population showed that comorbidity is the norm in adults with asthma, with 62.6% of people having one or more comorbidity. Of the 39 comorbidities evaluated, 36 (92.3%) occurred more often in people with asthma, including depression, anxiety, coronary heart disease, epilepsy, migraine and pain. Hypertension was the most prevalent physical condition identified in both groups, but still had one of the largest absolute percentage differences in prevalence in adults with asthma, with the others being COPD, depression, pain and dyspepsia. In relative terms however, the comorbidities most likely to be present in people with asthma compared to the general population were COPD, bronchiectasis, eczema, dyspepsia and chronic sinusitis.

Several studies have previously measured the prevalence of comorbidity in people with asthma. A Canadian claims-based study examined differences in comorbidity according to 14 disease categories reporting a 50% greater relative risk of comorbidity among those with asthma compared to those without.[17] A study from the United States found that 26% of people with asthma had one or more comorbidities whilst 10% had three or more, however this study only measured 5 comorbid conditions.[18] Similar findings were observed in a study from Germany examining only 8

comorbidities, which reported that 26% of people with asthma had at least one comorbidity and 17% had two or more conditions.[19] A greater proportion of patients in our study had at least one comorbidity suggesting that these studies may have underestimated the prevalence of comorbidity, in part due to the limited number of comorbidities included for evaluation.

Our study identified comorbidities associated with atopic asthma, such as eczema and chronic sinusitis. However in relative terms, the respiratory comorbidities most strongly associated with asthma were COPD, closely followed by bronchiectasis. Similar findings in terms of respiratory comorbidity were seen in a Canadian study and in a recent meta-analysis of observational studies.[20, 21] This association could in part be explained by asthma-COPD overlap syndrome (ACOS) that may be caused by long-term uncontrolled airway inflammation leading to airway remodelling and fixed airway obstruction, or as a result of COPD developing de novo in people with asthma who smoke.[22] These are both potentially modifiable risk factors to preserve respiratory function and reduce the risk of respiratory comorbidity in later life. With regards to bronchiectasis, people with asthma are at increased risk of lower respiratory tract infections including pneumonia that potentially contribute to the development of bronchiectasis.[17] Whilst the diagnosis of asthma is often clinical, we did not use objective measures such as lung function or CT scanning to differentiate between asthma and COPD or bronchiectasis because these data were not available. Due to the cross-sectional nature of our study, we cannot exclude the possibility of coding errors contributing to the observed associations and of some misclassification between diagnoses. Nevertheless, asthma is a recognised comorbidity in people with bronchiectasis as highlighted by a recent prospective international multicentre cohort study and asthma-COPD overlap syndrome is a well-recognised entity, with chronic diseases being generally well recorded with these types of data.[23] It therefore seems prudent to consider these respiratory comorbidities because they may require different treatment approaches or have differential risks of adverse effects from medication, such as the risk of pneumonia with inhaled corticosteroids.[24]

In contrast, the relationship between asthma and other common comorbidities is more complex. The association with reflux disease could result from increased diagnosis from closely related symptoms (such as cough) compounded by the use of medicines including oral steroids. Reflux is potentially an important comorbidity associated with an increased risk of asthma exacerbations due to direct airway contact with gastric acid triggering a vasovagal reflex and bronchospasm.[25] An association with hypertension may also be related to the use of chronic inhaled beta2-agonist stimulants or in part due to increased blood pressure screening during routine consultations for asthma, a feature that may also relate to other comorbidities.[26] The observed association between chronic pain and asthma is less understood with only a limited number of studies having been performed linking pain and asthma.[27]

Mental health conditions are particular important to consider and our study showed a significant association between asthma and several mental health comorbidities, including anxiety and depression. Although several international studies have shown depression to be approximately twice as common in people with asthma, less consistent associations have been reported with anxiety.[19][28][29] Indeed, previous work on multimorbidity has shown that the prevalence of mental health conditions rises as the number of comorbid conditions increases, particularly in people from more socioeconomically deprived backgrounds, suggesting that a holistic generalist approache to asthma care may be required.[14] However, in the UK at least, a perverse 'invers care law' in primary care funding persists with lower funding relative to multimorbidity burden in practices serving more deprived populations.[30][31]

After adjustment for other physical comorbidities, the probability of dementia was significantly lower in people with asthma than people without. To our knowledge, only one other study has assessed the relationship with dementia, reporting a similar sized association with as ours although not statistically significant (adjusted OR 0.64, 95% CI 0.28 to 1.48).[32] This association may partly be

related to the definition of asthma used in our study which included diagnostic coding and asthma treatment within 12 months of data extraction, and medication adherence could be less likely in people with dementia.

International asthma guidelines rely on the highest quality evidence to make recommendations on asthma care, much of which results from clinical trials. However, it is well recognised that people in clinical trials may not be representative of people with asthma in the general population. Our study shows that comorbidity is the norm in people with asthma yet it is rarely reported in important clinical trials. For example, the Salmeterol Multicenter Asthma Research Trial which assessed the risk of severe exacerbations in people with asthma provides no description of comorbidities among its participants.[33] Where comorbidities are reported, it is generally in relation to the exclusion of people with significant or serious comorbidities that may be unspecified, for example by excluding people with "any other significant medical illnesses".[34] Such exclusions and underreporting potentially affect the generalisability of such evidence which may differ in people with a range of comorbidities.[13]

This study has several strengths and limitations. A strength is the large representative population used for analysis with data obtained from routinely collected healthcare systems, at a time when GP practices were incentivised to keep an up to date register of people with asthma. An important limitation is that like other cross-sectional studies, it is only possible to examine associations rather than explore causality.[35] This study is reliant on the accuracy of clinical coding and GP electronic medical records may not accurately capture all relevant data on asthma such as airway variability. However, at the time of data extraction, general practices were financially incentivised to create and maintain an accurate register of people with asthma as well as many of the other comorbidities examined that was subject to external inspection by the NHS to ensure compliance with contractual requirements, with common chronic conditions in UK primary care data being well recorded.[36, 37]

The definition included the use of asthma controller medication and was based upon that used by the UK Quality and Outcomes Framework, a national pay for performance system which provides payment to GPs to keep registers of asthma patients included. This definition excludes those with a history of asthma in the past that no longer receive treatment, which are included in the non-asthma population. It was also not possible to measure the prevalence of some other comorbidities including NSAID-exacerbated respiratory disease which occurs in approximately 9-10% of patients with asthma, and for which selective COX-2 inhibitors may be more appropriate in people requiring NSAIDs for the treatment of certain comorbidities such as pain and arthritis. [38][39] Finally, further analytical work examining the impact of comorbidities on asthma severity, control and health care costs is still required for several comorbidities.

In conclusion, this study highlights the significantly greater prevalence of comorbidity in people with asthma that clinicians should be aware when reviewing people with asthma. Further studies are required to assess the generalizability of evidence in comorbid people with asthma and to evaluate generalist approaches to asthma care.

Acknowledgments

CW was supported by an NHS Education for Scotland Clinical Academic Fellowship and DM was supported by a University of Dundee Discovery Fellowship. The data set creation was supported by Scottish Government Chief Scientist Office Applied Research Programme Grant 07/01.

Author contributions

Conceived the analysis: CW, DM, SM, BG. Created the dataset: BG, SM. Analyzed the data: CW, DM. Interpreted the findings: CW, DM, SM, BG. Wrote the manuscript: CW, DM, SM, BG.

Conflict of interest

The authors declare they have no conflict of interests.

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2012.

2. QOF database 2016. Asthma. Available at: https://www.gpcontract.co.uk/browse/UK/Asthma/16. (Accessed 01.01.2017).

3. Morrison D, Agur K, Mercer S, et al. Managing multimorbidity in primary care in patients with chronic respiratory conditions. NPJ Prim Care Respir Med 2016;**26**:16043.

4. Morales DR, Dreischulte T, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blocker eye drops in asthma: population-based study and meta-analysis of clinical trials. *Br J Clin Pharmacol.* 2016; **82**:814-22.

5. Goodwin RD, Scheckner B, Pena L, et al. A 10-year prospective study of respiratory disease and depression and anxiety in adulthood. Ann Allergy Asthma Immunol 2014;**113**(5):565-70.

6. Morales DR, Jackson C, Lipworth BJ, et al. Adverse respiratory effect of acute beta-blocker exposure in asthma: a systematic review and meta-analysis of randomized controlled trials. Chest 2014;**145**(4):779-86.

7. Morales DR, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blockers in people with asthma and cardiovascular disease: population based nested case control study. *BMC Medicine* 2017; 2017; **15:** 18.

8. Eisner MD, Katz PP, Lactao G, et al. Impact of depressive symptoms on adult asthma outcomes. Ann Allergy Asthma Immunol 2005;**94**(5):566-74.

9. Thomas M, Bruton A, Moffat M, et al. Asthma and psychological dysfunction. Prim Care Respir J 2011;**20**(3):250-6.

10. Skapinakis P, Lewis G, Araya R, et al. Mental health inequalities in Wales, UK: multi-level investigation of the effect of area deprivation. Br J Psychiatry 2005;**186**:417-22.

11. Travers J, Marsh S, Williams M, et al. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? Thorax 2007;**62**(3):219-23.

12. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. Chest. 2004;125:2309-21.

13. Elder R, Kirkpatrick M, Ramsay W, Macleod M, Gurthrie B, Sutton M, Watt G. Measuring quality in primary medical services using data from SPICE. Edinburgh: Information and Statistics Division, NHS National Services Scotland; 2007. Available: http://www.em-online.com/download/medical_article/36074_spice_report_july_2007.pdf. Accessed 20/04/2017.

14. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012;**380**(9836):37-43.

15. Carstairs V, Morris R. Deprivation and health in Scotland. Health Bull (Edinb) 1990;**48**(4):162-75.

16. McLean G, Guthrie B, Watt G, et al. Practice postcode versus patient population: a comparison of data sources in England and Scotland. Int J Health Geogr 2008;**7**:37.

17. Gershon AS, Guan J, Wang C, et al. Describing and quantifying asthma comorbidity [corrected]: a population study. PLoS One 2012;**7**(5):e34967.

18. Patel MR, Janevic MR, Heeringa SG, et al. An examination of adverse asthma outcomes in U.S. Adults with multiple morbidities. Ann Am Thorac Soc 2013;**10**(5):426-31.

19. Steppuhn H, Langen U, Keil T, et al. Chronic disease co-morbidity of asthma and unscheduled asthma care among adults: results of the national telephone health interview survey German Health Update (GEDA) 2009 and 2010. Prim Care Respir J 2014;**23**(1):22-9.

20. Prosser R, Carleton B, Smith A. The comorbidity burden of the treated asthma patient population in British Columbia. Chronic Dis Can 2010;**30**(2):46-55.

21. Su X, Ren Y, Li M, Zhao X, Kong L, Kang J. Prevalence of Comorbidities in Asthma and Nonasthma Patients: A Meta-analysis. Medicine (Baltimore). 2016;**95**(22):e3459.

22. Nielsen M, Barnes CB, Ulrik CS. Clinical characteristics of the asthma-COPD overlap syndrome--a systematic review. Int J Chron Obstruct Pulmon Dis 2015;**10**:1443-54.

23. McDonnell MJ, Aliberti S, Goeminne PC, Restrepo MI, Finch S, Pesci A, Dupont LJ, Fardon TC, Wilson R, Loebinger MR, Skrbic D, Obradovic D, De Soyza A, Ward C, Laffey JG, Rutherford RM, Chalmers JD. Comorbidities and the risk of mortality in patients with bronchiectasis: an international multicentre cohort study. Lancet Respir Med. 2016;**4**:969-979.

24. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2014(3):CD010115.

25. Price D, Wilson AM, Chisholm A, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. J Asthma Allergy 2016;**9**:1-12.

26. Christiansen SC, Schatz M, Yang SJ, et al. Hypertension and Asthma: A Comorbid Relationship. J Allergy Clin Immunol Pract 2016;**4**(1):76-81.

27. Lunardi AC, Marques da Silva CC, Rodrigues Mendes FA, et al. Musculoskeletal dysfunction and pain in adults with asthma. J Asthma 2011;**48**(1):105-10.

28. Garin N, Olaya B, Perales J, et al. Multimorbidity patterns in a national representative sample of the Spanish adult population. PLoS One 2014;**9**(1):e84794.

29. Scott KM, Von Korff M, Ormel J, et al. Mental disorders among adults with asthma: results from the World Mental Health Survey. Gen Hosp Psychiatry 2007;**29**(2):123-33.

30. McLean G, Guthrie B, Mercer SW, Watt GCM. General Practice payment systems underpin the persistence of the inverse care law. BJGP 2015;**65**:e799-805

31. Smith DJ, Court H, McLean G, Martin D, Langan Martin J, Guthrie B, Gunn J, Mercer SW. Depression and multimorbidity: cross-sectional study of 1,751,841 patients in primary care. The Journal of Clinical Psychiatry 2014, 75(11): 1202-1208

32. Eriksson UK, Gatz M, Dickman PW, et al. Asthma, eczema, rhinitis and the risk for dementia. Dement Geriatr Cogn Disord 2008;**25**(2):148-56.

33. Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;**129**(1):15-26.

34. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med 2010;**363**(18):1715-26.

35. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J 2003;**20**(1):54-60.

36. NHS Primary care contracting. QOF 5% Random Counter Fraud Checks. 2007. Available at: https://www.pcc-cic.org.uk/sites/default/files/articles/attachments/pct_briefing_note_qof_5_checks_v7_08_05_07.pdf. Accessed 20/04/2017.

37. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010 Jan;69(1):4-14.

38. Morales DR, Guthrie B, Lipworth BJ, Jackson C, Donnan PT, Santiago VH. NSAID-exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. Allergy. 2015;**70**(7):828-35.

39. Morales DR, Lipworth BJ, Guthrie B, Jackson C, Donnan PT, Santiago VH. Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: Meta-analysis of controlled clinical trials. J Allergy Clin Immunol. 2014;**134**(1):40-5.

Table 1: **Characteristics of adults with and without asthma in the dataset**

	Adults with asthma No. (%) (N=84505)	Adults without asthma No. (%) (N=1339873)	Percentage difference (95% CI)
Sex			
▪ Male	34862 (41.3)	664567 (49.6)	-8.3 (-8.0 to -8.7)
▪ Female	49643 (58.7)	675306 (50.4)	8.3 (8.0 to 8.7)
Smoking Status			
▪ Non-smoker	42206 (49.9)	643641 (48.0)	1.9 (1.6 to 2.3)
▪ Ex-smoker	20604 (24.4)	231448 (17.3)	7.1 (6.8 to 7.4)
▪ Smoker	20914 (24.7)	328403 (24.5)	0.2 (0.1 to 0.5)
▪ Missing	781 (0.9)	136381 (10.2)	-9.3 (-9.2 to -9.3)
Age Group (years)			
▪ 18 to 24	8269 (9.8)	143424 (10.7)	-0.9 (-0.7 to -1.1)
▪ 25 to 44	28573 (33.8)	479816 (35.8)	-2.0 (-1.7 to -2.3)
▪ 45 to 64	28661 (33.9)	444466 (33.2)	0.7 (0.4 to 1.1)
▪ 65 to 84	17285 (20.5)	237315 (17.7)	2.7 (2.5 to 3.0)
▪ 85 and over	1717 (2.0)	34852 (2.6)	-0.6 (-0.5 to -0.7)
Deprivation (quintiles)			
▪ Q1 (least deprived)	14799 (17.5)	257230 (19.2)	-1.7 (-1.4 to -2.0)
▪ Q2	17292 (20.5)	286862 (21.4)	-1.0 (-0.6 to -1.2)
▪ Q3	19473 (23.0)	302774 (22.6)	0.5 (0.2 to 0.7)
▪ Q4	17154 (20.3)	254230 (19.0)	1.3 (1.1 to 1.6)
▪ Q5 (most deprived)	15787 (18.7)	238777 (17.8)	0.9 (0.6 to 1.1)
No. of total comorbidities			
▪ None	31577 (37.4)	721362 (53.8)	-16.5 (-16.1 to -16.8)
▪ One	18506 (21.9)	269417 (20.1)	1.8 (1.5 to 2.1)
▪ Two	12188 (14.4)	145991 (10.9)	3.5 (3.3 to 3.8)
▪ Three	8449 (10.0)	86943 (6.5)	3.5 (3.3 to 3.7)
▪ Four or more	13785 (16.3)	116160 (8.7)	7.6 (7.4 to 7.9)
No. of physical comorbidities			
▪ None	37083 (43.9)	800108 (59.7)	-15.8 (-15.5 to -16.2)
▪ One	19167 (22.7)	256230 (19.1)	3.6 (3.3 to 3.9)
▪ Two	11585 (13.7)	130557 (9.7)	4.0 (3.7 to 4.2)
▪ Three	7258 (8.6)	72832 (5.4)	3.2 (3.0 to 3.4)
▪ Four or more	9412 (11.1)	80146 (6.0)	5.2 (4.9 to 5.4)
No. of mental health comorbidities			
▪ None	64949 (76.9)	1138705 (85.0)	-8.1 (-7.8 to – 8.4)
▪ One	16119 (19.1)	167699 (12.5)	6.6 (6.3 to 6.8)
▪ Two or more	3437 (4.1)	33469 (2.5)	1.6 (1.4 to 1.7)

(Total number of comorbidities = Number of physical comorbidities + Number of mental comorbidities)

Table 2: **Prevalence of comorbid physical conditions in people with and without asthma.**

Physical health conditions	Adults with asthma No. (%) (N=84505)	Adults without asthma No. (%) (N=1339873)	Unadjusted OR (95% CI)	Adjusted for age, sex, deprivation, smoking OR (95% CI)
COPD	11345 (13.4)	41762 (3.1)	4.82 (4.72 to 4.93)	5.65 (5.52 to 5.79)
Bronchiectasis	660 (0.8)	2154 (0.2)	4.89 (4.48 to 5.34)	4.65 (4.26 to 5.08)
Eczema or psoriasis	1766 (2.1)	8603 (0.6)	3.30 (3.14 to 3.48)	3.30 (3.14 to 3.48)
Dyspepsia (treated)	9251 (10.9)	69953 (5.2)	2.23 (2.18 to 2.28)	2.20 (2.15 to 2.25)
Chronic sinusitis	1117 (1.3)	8048 (0.6)	2.22 (2.08 to 2.36)	2.12 (1.99 to 2.26)
Pain	13431 (15.9)	112700 (8.4)	2.06 (2.02 to 2.10)	2.04 (1.99 to 2.08)
Migraine	1131 (1.3)	8120 (0.6)	2.23 (2.09 to 2.37)	1.97 (1.85 to 2.10)
Diverticular disease	3121 (3.7)	30692 (2.3)	1.64 (1.58 to 1.70)	1.63 (1.57 to 1.70)
Viral hepatitis	104 (0.1)	1071 (0.1)	1.54 (1.26 to 1.88)	1.95 (1.59 to 2.38)
Irritable bowel syndrome	4968 (5.9)	47169 (3.5)	1.71 (1.66 to 1.76)	1.57 (1.53 to 1.62)
Constipation	3317 (3.9)	33099 (2.5)	1.61 (1.56 to 1.67)	1.57 (1.51 to 1.63)
Heart Failure	1539 (1.8)	17360 (1.3)	1.41 (1.34 to 1.49)	1.47 (1.39 to 1.55)
Inflammatory bowel disease	827 (1.0)	8924 (0.7)	1.47 (1.37 to 1.58)	1.42 (1.32 to 1.53)
Rheumatological disease	4803 (5.7)	53205 (4.0)	1.46 (1.41 to 1.50)	1.41 (1.37 to 1.46)
Coronary heart disease	6103 (7.2)	75364 (5.6)	1.31 (1.27 to 1.34)	1.39 (1.35 to 1.43)
Prostate	1045 (1.2)	14188 (1.1)	1.41 (1.33 to 1.51)	1.32 (1.24 to 1.41)
Thyroid	6076 (7.2)	65867 (4.9)	1.50 (1.46 to 1.54)	1.33 (1.30 to 1.37)
Diabetes	5727 (6.8)	69104 (5.2)	1.34 (1.30 to 1.38)	1.31 (1.28 to 1.35)
Epilepsy	953 (1.1)	11431 (0.9)	1.33 (1.24 to 1.42)	1.29 (1.21 to 1.38)
Hypertension	16986 (20.1)	217328 (16.2)	1.30 (1.28 to 1.32)	1.27 (1.25 to 1.30)
Deafness	3952 (4.7)	50782 (3.8)	1.25 (1.21 to 1.29)	1.22 (1.18 to 1.27)
Chronic kidney disease	2427 (2.9)	31139 (2.3)	1.24 (1.19 to 1.30)	1.23 (1.17 to 1.28)
Atrial fibrillation	1642 (1.9)	222334 (1.7)	1.17 (1.11 to 1.23)	1.21 (1.15 to 1.28)
Glaucoma	1111 (1.3)	14808 (1.1)	1.19 (1.12 to 1.27)	1.18 (1.11 to 1.26)
Chronic liver disease	175 (0.2)	2439 (0.2)	1.14 (0.98 to 1.33)	1.27 (1.09 to 1.48)
Blindness	582 (0.7)	7796 (0.6)	1.19 (1.09 to 1.29)	1.16 (1.06 to 1.26)
Peripheral vascular disease	1601 (1.9)	21639 (1.6)	1.18 (1.19 to 1.24)	1.20 (1.14 to 1.26)
Stroke or TIA	2341 (2.8)	34204 (2.6)	1.09 (1.04 to 1.14)	1.10 (1.06 to 1.15)
Cancer diagnosis within 5 yr.	2863 (3.4)	40801 (3.0)	1.12 (1.07 to 1.16)	1.07 (1.03 to 1.11)
Parkinson's Disease	151 (0.2)	2590 (0.2)	0.92 (0.78 to 1.09)	0.94 (0.80 to 1.11)
Multiple sclerosis	205 (0.2)	3642 (0.3)	0.89 (0.78 to 1.03)	0.83 (0.72 to 0.96)

Rheumatological disease = Gout, inflammatory arthritis and connective tissue disease.

Table 3: **Prevalence of comorbid mental health conditions in people with and without asthma**

Mental health conditions	Adults with asthma No. (%) (N=84505)	Adults without asthma No. (%) (N=1339873)	Unadjusted OR (95% CI)	Adjusted for age, sex, smoking, and deprivation OR (95% CI)	Adjusted for age, sex, deprivation, no. physical conditions, smoking OR (95% CI)
Depression	14626 (17.3)	129317 (9.1)	1.96 (1.92 to 2.00)	1.86 (1.82 to 1.90)	1.60 (1.57 to 1.63)
Anxiety and other neurotic stress related and somatoform disorders	5820 (6.9)	49906 (3.7)	1.91 (1.86 to 1.97)	1.85 (1.80 to 1.90)	1.53 (1.48 to 1.57)
Alcohol problem	3339 (4.0)	39024 (2.9)	1.37 (1.32 to 1.42)	1.65 (1.59 to 1.71)	1.47 (1.42 to 1.53)
Anorexia or bulimia	436 (0.5)	4870 (0.4)	1.42 (1.29 to 1.57)	1.31 (1.19 to 1.44)	1.18 (1.07 to 1.30)
Drug & medication use problem	3450 (4.1)	39010 (2.9)	1.42 (1.37 to 1.47)	1.53 (1.47 to 1.58)	1.25 (1.21 to 1.30)
Schizophrenia or bipolar disorder	891 (1.1)	11602 (0.9)	1.22 (1.14 to 1.31)	1.26 (1.17 to 1.35)	1.18 (1.10 to 1.27)
Learning disability	375 (0.4)	4639 (0.3)	1.28 (1.16 to 1.43)	1.24 (1.12 to 1.38)	1.09 (0.98 to 1.21)
Dementia	446 (0.5)	11250 (0.8)	0.63 (0.57 to 0.69)	0.64 (0.58 to 0.70)	0.60 (0.55 to 0.66)